DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 27 2004

Mr. Robert Cohen
560 Oradell Avenue
Oradell, NJ 07649

Re: Docket 94P-0343

Dear Mr. Cohen:

This is the final response from the Food and Drug Administration (FDA) to your Citizen Petition dated September 9, 1994, and subsequently amended. The petition requests that the Commissioner of Food and Drugs revoke the use of recombinant bovine growth hormone (rbGH, also known as bovine somatotropin (bST)) or Posilac®, sponsored by the Monsanto Corporation and approved by the FDA for use in dairy cattle.

We have thoroughly reviewed the issues that you raised in your petition as amended. We believe that these issues were essentially duplicated in the Citizen Petition you submitted October 21, 1999 (99P-4613), which also requested withdrawal of Posilac from the market. The issues raised in your 1999 petition were addressed in my letter to you of April 20, 2000, which denied your 1999 petition.

One matter that was addressed in your 1994 petition, Docket 94P-0343, was not specifically discussed in our denial of your 1999 petition. That matter concerned an increase in spleen weights of test animals that had been administered rbGH. Your 1994 petition alleged that this increase in spleen weights raised concerns that rbGH might be carcinogenic. My April 20, 2000 letter addressed the carcinogenic properties of rbGH generally, but did not discuss test animal spleen weights. Our position on this specific topic is explained below.

For the reasons explained in my April 20, 2000 letter and as elaborated below, we are denying your 1994 petition, Docket 94P-0343.

1994 Petition History

Your petition (94P-0343) was filed on September 16, 1994. The ground for the requested revocation of the use of rbGH was what you contended to be a "new problem" found in an article published in Science in 1990.[1] According to your petition, table 2 in that article indicates significant biological effects from the oral ingestion and subcutaneous injection of rbGH. As supporting evidence, you pointed out that the table shows a mean 8.28% increase in spleen weight of male test animals from oral ingestion, in addition to 39.69 and 46.15%

[1] Juskevich, J.C. and C.G. Guyer, "Bovine Growth Hormone: Human Food Safety Evaluation, Science, Vol. 249, pp. 875-883 (August 24, 1990)

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increases in male and female spleens, respectively, following subcutaneous injection.[2] According to your petition, abnormal spleen growth can indicate carcinogenicity concerns, specifically a pre-leukemia state. You stated that toxicological studies were needed but had not been required by FDA because the agency concluded that there was no biological effect from the oral ingestion of rbGH.

You amended the 1994 petition with a submission dated November 10, 1994. In the amendment, you challenged a number of FDA conclusions related to use of rbGH in dairy cattle. You asserted, among other things, that (1) rbGH has biological effects on test animals, citing the data on animal spleen weights contained in the original petition; (2) that treatment of cows with rbGH increases the level of insulin-like growth factor (IGF-1) in cow's milk; and (3) that IGF-1 is not broken down in the gastrointestinal system or eliminated by pasteurization as claimed by FDA.

The November 10, 1994 petition amendment elaborated on the carcinogenic concerns raised in the original petition. The document claimed that IGF-1 has been identified as an autocrine and endocrine growth regulator that accelerates various types of carcinomas. The petition amendment cited a large number of scientific publications to support the views expressed in it.

You then submitted another document dated November 14, 1994, which essentially repeated the information contained in the November 10, 1994 petition amendment.

On July 31, 1995, you supplemented the 1994 petition in a letter faxed to Richard Arkin of the FDA Center for Veterinary Medicine (CVM). In it, you disputed the conclusion in the 1990 Science article that at least 90% of rbGH activity is destroyed upon pasteurization of milk, claiming that only 19% was destroyed. You reiterated your position that rbGH is orally active, and that administration of the drug to dairy cattle increases IGF-1 levels in milk. You also raised a new issue: that the marketed product (Posilac) is not the same drug that was tested because of differences in amino acids. Your letter also stated that because FDA did not release data from a 1989 Searle report pursuant to a request under the Freedom of Information Act (FOIA), the agency was applying 'trade protection' incorrectly. However, in a Letter Order issued November 25, 1996, the United States District Court, District of New Jersey, found that FDA was not required to release this data under FOIA or FDA's own statutes.

On August 10, 1995, Dr. Richard Teske, then CVM's Acting Associate Director for Policy, wrote to you, summarizing the explanations given to you in an April 21, 1995 meeting with you at CVM. His letter addressed amino acid differences between the test and marketed products; IGF-1 levels in milk following administration of rbGH, and the fact that little or no absorption of IGF-1 takes place; and the effect of rbGH on spleen weights in test animals.

Your August 16, 1995 response disputed the positions expressed in Dr. Teske's letter, and reiterated your previously stated position as to the effects of pasteurization on rbGH levels in milk.

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[2] Data in Table 2 are from "Three-Month (90 day) Oral Toxicity Study of Sometribove in the Rat," a study subsequently extended to 180 days and conducted by Monsanto in support of the approval of Posilac.

Response to the 1994 Petition

As I stated above, your October 21, 1999 petition (99P-4613) raised essentially the same issues as your 1994 petition with its amendments. In the 1999 petition, you contended that (1) a new study reported an increase in serum levels of IGF-1 in humans following milk consumption, representing absorption of dietary IGF-1; (2) Monsanto changed the manufacturing process for rbGH after studies supporting the New Animal Drug Application (NADA) were completed, resulting in a different product that invalidated the research used to support the approval; (3) the sponsor's 90-day toxicology study and/or the information derived from the additional 90 days of the study demonstrated both that rbGH is absorbed and is not safe; and (4) rbGH survives the pasteurization process and thus is available for absorption.

Our April 20, 2000 denial of petition 99P-4613 responded to the major issues raised in your 1994 petition. We will not repeat in detail the explanations provided in the denial of petition 99P-4613, since it was addressed to you, but will instead incorporate its content by reference in this denial.

However, we will summarize major points made in the denial letter as follows: Levels of IGF-1 in milk, whether or not from rbGH-supplemented cows, are not significant when compared with the levels of endogenously produced IGF-1 in humans (p.2). Monsanto's manufacturing changes resulted in only biologically inconsequential variations in the product used in the safety and effectiveness studies and, therefore, the rbGH product FDA approved is the same as the product used in the studies (p. 5). Based on a review of the literature, there is no evidence linking rbGH to increased cancer risks (p. 5). No adverse effects were observed following Monsanto's 180-day toxicology study (p. 9). Finally, digestive enzymes in the gastrointestinal tract degrade rbGH, and therefore rbGH is not absorbed intact (p. 8).

As I noted above, your original 1994 petition expressed the view that the increased spleen weight observed in rats fed rbGH in the Monsanto toxicology study raised a question about the tumor-producing potential of rbGH. In responding to your 1999 petition, we reviewed the available evidence related to the carcinogenicity of rbGH and IGF-1 and, as summarized above, concluded that the concerns you expressed were unfounded. Because the April 2000 denial letter did not specifically address the spleen weight issue, however, we will do so in this letter.

The spleen weight data, considered in the context of all available evidence concerning the carcinogenic properties of rbGH and IGF-1, do not raise carcinogenicity concerns. Because there was no dose-response effect associated with the increased spleen weights following oral administration of rbGH, we conclude that the effect on spleen weights was not biologically significant. An increase in body weight is the most consistent weight parameter for measuring the effect of growth hormones in rats. Even at the highest dose, there was no increase in body weight due to oral treatment of rbGH in the toxicology study. Your petition notes that spleen weights increased following subcutaneous injection (as distinguished from oral ingestion), but does not place emphasis on these data in support of the petition.

De-emphasis of these numbers is appropriate because, among other reasons, rbGH is not absorbed intact.

Conclusion

For the reasons stated above, FDA denies your Citizen Petition requesting withdrawal of the approval of the New Animal Drug Application providing for the marketing of Posilac by Monsanto.

Sincerely yours,

John M. Taylor, III
Associate Commissioner
for Regulatory Affairs

cc: HFA-305 (Docket 94P-0343)